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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53 and 56-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53 and 56-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 4/25/2006, and a response to the arguments is set forth.

2. Claims 1-41, 54 and 55 have been cancelled.

4. Claims 42 and 56-60 have been amended.

5. Claims 68-78 have been newly added.

6. Claims 42-53 and 56-78 are under examination.

7. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

8. In view of the papers filed 03/06/2006, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed, such that Dr. Alfred D. Steinberg and Dr. Dennnis Klinman are added as inventors in the instant application.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Rejections Withdrawn

9. The rejection of claims 42-58, 66 and 67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendments to the claims.

10. The rejection of claims 47-65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6653292 (Krieg and Weiner). A Terminal Disclaimer was filed on 03/06/2006, and has been approved on 06/30/2006.

Rejections Maintained

11. The rejection of claims 42-67 and 68-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained and made here within.

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph on 4/25/2006 are carefully considered, but not found to be persuasive for the reasons below.

The applicants argue (page 10 of the response, in particular) that claim 42 has been amended to recite additional limitations such as the length of the oligonucleotide and that the oligonucleotide has a phosphate backbone modification and thus the claims encompass a well defined class of molecules, CpG containing oligonucleotides,

which Applicant has demonstrated produce an immune response consistent with the treatment of cancer. Further, the applicants argue that the teachings of Agarwal et al do not demonstrate that the claimed invention was unpredictable at the time of the invention and that all unmethylated CpG oligonucleotides don't work for stimulating an immune response..... and thus the discussion presented by Agarwal et al do not demonstrate the unpredictability of the class of CpG oligonucleotides (page 11 of the response, in particular). Applicants argue that the specification discloses an unmethylated CpG dinucleotide provoke an immune response is consistent with the treatment of cancer and other disease.....data is present in vitro and in vivo using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement....." (pages 11-12, bridging paragraph). Applicants state that CpG containing oligonucleotide mimic bacterial DNA ..... Host DNA, and that the data need not support that every CpG oligonucleotide work equivalently or even work at all" (page 12 in particular). Applicant cite MPEP section 2164.05(a) that the examiner should not use post-filing references to demonstrate that the patent is non-enabling.....instead it describes years worth of post-filing date studies that have focused on optimization techniques and developing optimized products" (page 13, 2nd paragraph in particular). Applicants further argue that the since the fact the CpG oligonucleotides do not cross the blood brain barrier and don't have significant oral bioavailability is not essential to the invention.....and thus the potential toxicity was not sufficient to stop the administration of these compounds to humans" (pages 13-14 bridging paragraph, in particular). The applicant argues that "the specification includes in vitro data on mouse

and human cells, as well as in vivo data.....confirming that the pattern of cytokine release and Th1 effects could be exploited in vivo.

In response to the above arguments, it is noted that claim 42 is amended to include the limitation of CpG being "unmethylated" and having "a phosphate backbone", however it is recognized in the art (as stated in the previous office action), there exists a high unpredictability of using CpG molecules in the treatment of cancer in humans. Agarwal et al does say that that the studies on the medicinal chemistry of CpG DNA have just begun.....further fine-tuning the immunomodulatory effects" as stated by the applicant on pages 11 and 12; and it is noted that Agarwal is in compliant with the specification that the in vitro bacterial and synthetic CpG have DNA mitogenic effects on B cell.....and an increases number of immunoglobulin-producing cells", however, such arguments are irrelevant to the scope of the invention. The claimed invention is drawn to "a method of treatment for treating cancer, comprising administering to a human ...CpG....". Thus, contrary to the applicants arguments, Agarwal et al does support the unpredictability in the art of by teaching that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known. Applicants argue that "eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG containing olinucleotides" and hence the claimed invention meets the enablement requirement for the claimed

invention (page 12, in particular). In response to this, the applicant is reminded that due the high level of skill in the art (as agreed by the applicant on page 16), it is nearly impossible to predict the claimed invention from the information provided in the specification. Further, the argument (page 13, in particular) that the teachings of Crooke et al does not demonstrate the unpredictability of using a phosphorothioate CpG oligonucleotide in the methods of the invention is not found persuasive. The fact that the CpG oligonucleotide does not cross the blood brain barrier is relevant and important to the claimed invention, because claim 45 is drawn to a method of treating brain cancer, and further Crooke et al further show that the release of cytokines, activation of complement and interference with clotting clearly poses dose limits if they are encountered in the clinic.

The applicants argue that "the specification includes in vitro data on mouse and human cells, as well as in vivo data.....confirming that the pattern of cytokine release and Th1 effects could be exploited in vivo"..... for instance...the data described in Kim et al..... toxic effects that would halt further human trials were not observed....." (pages 14-15 in particular). Further, the arguments presented in the "quantity of experimentation" wherein the applicant states that specification provides a description of a class of molecules, how to make such molecules..... a teaching that such molecules are useful in the treatment of cacner..... applicants have shown throughtout the

specification using actual working examples and numerous CpG oligonucleotides that these molecules stimulate an immune response."

In response to the above arguments, the applicant is pointed to the studies below as described below:

The specification is viewed merely as an invitation to one skilled in the art to develop the claimed invention. As the court stated in:

> As we stated in *Genentech*:
>
> Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
>
> *See Genentech*, 108 F.3d at 1366, 42 USPQ2d at 1005. We thus conclude that the district court did not clearly err in finding that the specifications provided little guidance or direction as to the practice of antisense in cells other than *E. coli*, and that such minimal disclosure as there was constituted no more than a plan or invitation to practice antisense in those cells.

Id. at 1138. Here, however, the specification provides comparably little disclosure, failing to disclose any guidance, direction, or working examples.

Supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to

satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to treat cancer comprising administering to a human subject a CpG immunostimulatory oligonucleotide having an unmethylated CpG dinulecotide; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that

"[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer vaccines to attenuate cancer has been met with very little success. In addition to references cited in preceding Office actions, which also describe such disappointing results and attribute the lack of success

to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunisation can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that

found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

Thus, in conclusion, the applicant is again reminded that the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide; the breadth of the claims as mentioned above; the limited number of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed vaccine composition is undue.

Thus, The instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the claims. One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects.

Conclusion

12. No claims are allowed.

13. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi Ph.D.
(571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER